STUDIES ON ASYMMETRY OF THE CITRIC ACID TYPE

BY

PEARL SCHWARTZ

B.A., Barnard College, 1935

M.A., Columbia University, 1938

AN ABSTRACT OF A

THESIS

SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS

FOR THE DEGREE OF DOCTOR OF PHILISOPHY IN CHEMISTRY

IN THE GRADUATE COLLEGE OF THE

UNIVERSITY OF ILLINOIS, 1952

URBANA, ILLINOIS

STUDIES ON ASYMMETRY OF THE CITRIC ACID TYPE

BY

PEARL SCHWARTZ

B.A., Barnard College, 1935

M.A., Columbia University, 1938

AN ABSTRACT OF A

THESIS

SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS

FOR THE DEGREE OF DOCTOR OF PHILISOPHY IN CHEMISTRY

IN THE GRADUATE COLLEGE OF THE

UNIVERSITY OF ILLINOIS, 1952

URBANA, ILLINOIS

ACKNOWLEDGMENT

Dr. H. E. Carter has suggested both the problem of this investigation and the interpretation of "citric acid asymmetry." The writer would like to express her gratitude for this, and also for his friendly interest in the work.

The microanalyses were performed by Mrs. Esther Fett, Mrs. Katherine Pih and Mr. Joseph Nemeth.

R. UNIV. BIBLIOTHEEK LEIDEN

STUDIES ON ASYMMETRY OF THE CITRIC ACID TYPE

Introduction

In the citric acid molecule, $HOOCCH_2$-C(OH)COOH-CH_2COOH, of the two CH_2COOH groups, only the group derived from oxaloacetate, and not that derived from acetate, takes part in enzymatic dehydration to cisaconitate. Here, the citric acid molecule, although it has a plane of symmetry and is therefore optically inactive, has reacted asymmetrically with an asymmetric reagent. Hence, it was of interest to find out, by the use of model compounds of the same type, namely C(AABD), whether, in a simple, non-enzymatic, homogeneous system, as well, one of the two structurally similar, but configurationally antipodal, groups might not also react preferentially with an optically pure, asymmetric reagent, to produce, *at equilibrium*, unequal amounts of the two diastereoisomers, $\overset{*}{C}$ (A$\overset{*}{E}$BD). To this end, it was decided to study the reaction of *beta*-phenylglutaric anhydride with optically active amines. This reaction was of particular interest, because no undisputed examples of this type of asymmetric synthesis are to be found in the literature. Use of an anhydride as the model compound offered the important advantage that the initial attack at one anhydride linkage does not leave the corresponding linkage available for a second attack; consequently, no di-substituted by-product is formed, to reduce the yield of the desired mono-substituted compound.

Discussion of Results

Beta-phenylglutaric anhydride (m.p. 105-106.5°) was prepared, with an over-all yield of 45%, by condensation of ethyl acetoacetate and benzaldehyde, in the presence of piperidine as catalyst, to form ethyl benzylidene*bis*acetoacetate. This compound was then hydrolyzed with hot concentrated aqueous potash and acidified, to give free *beta*-phenylglutaric acid. The acid was dehydrated by being refluxed for several hours with acetic anhydride.

Dextro-desoxyephedrine, when added in equimolecular proportions, to a benzene solution of *beta*-phenylglutaric anhydride, reacted rapidly and exothermically, to form N-methyl, N (*alpha*-phenyl)-*beta*-isopropyl-*beta*-phenylglutaramic acid, with a yield of 84-89% (N. E., 344-346; calculated, 340). The product did not crystallize readily, but only after much manipulation. The crude mixture was purified to the correct neutral equivalent, with 94% recovery, by solution in 1N NaOH, followed by extraction of free amine with benzene and acidification of the aqueous layer with concentrated HCl. The neutral equivalent of this product was 339.5; its specific rotation was —33.4° to —33.5° (5%, in methanol, 22-27°).

The preliminary fractionation of the two diastereoisomers was accomplished, quickly and reproducibly, in a very simple manner, by agitation of the intact product, ground to pass a No. 20 sieve, with ten volumes of ether, for ten seconds, followed by rapid filtration through an over-sized Buechner funnel, under slight suction. From the residue, the less soluble isomer was then obtained pure by repeated recrystallization

from eight to ten volumes of ethyl acetate. This form was obtained as prisms, melting at 132-133°, and having a specific rotation of —47.2° to —47.3° (5%, in methanol, 22-27°).

The more soluble isomer was obtained in a crude state by dilution of the filtrate from the "quick extraction" with an equal volume of ether. The solution, after standing overnight in a cold bath (—25° to —35°), deposited about one-fifth of the total solute as a crystalline crust, melting from 104° to 117°. Four additional recrystallizations from forty-five volumes of ether, raised the melting point to 121-122°, with a recovery in each step of about one-third. The specific rotation of the more soluble isomer (5%, in methanol, 22-27°) was —21.5° to —21.7°.

The percentage composition of the unfractionated mixture was determined from the specific rotations of the two isomers and that of the purified mixture. The two isomers were found to be present in approximately equal amounts.

The reaction of *levo-alpha*-phenethyl amine and *beta*-phenylglutaric anhydride was carried out in the same manner. In this case, the product crystallized rapidly, and was obtained with a yield of 93-95%, and gave the correct neutral equivalent and elementary analysis. Its specific rotation (2.5%, in methanol, 27-32°) was —69.5° to —70.0°. The mixture was then fractionated, ground as before, by being shaken for fifteen seconds with twenty volumes of warm (35°) ethyl acetate and then filtered rapidly. The less soluble isomer, obtained from the residue by repeated recrystallization from thirty volumes of ethyl acetate, melted at 184.5-185.5° and

had a specific rotation (2.5%, in methanol, 27-32°) of —83.1° to —83.5°.

The more soluble isomer could not be obtained from the filtrate of the "quick extraction" by uncontrolled recrystallization; invariably, mixed crystals of rather constant composition (m.p. 151-153°; specific rotation, —62° to —63°) were obtained. However, this isomer was isolated by the following procedure of "alternate crystallization." The filtrate, diluted to about 1.4% concentration, upon standing at 6°, seeded with a little of the less soluble isomer (Isomer A), slowly deposited a crop of crystals rich in this isomer. The supernatant, concentrated to about four-fifths volume, under similar conditions, deposited a crop of crystals rich in the more soluble isomer (Isomer B), melting from 150° to 165°. From this supernatant, similarly concentrated, and seeded with Isomer A, was obtained a second crop of crystals of crude Isomer A. This supernatant, concentrated in the same way, then gave a second crop of crystals rich in Isomer B. These steps were continued until about two grams of B-enriched crystals had been collected. This material, recrystallized from seventy volumes of ethyl acetate, yielded about 0.2 g. of the pure isomer (m.p. 168.5-169.5°; specific rotation, —49.2° to —49.5°, 2.5%, in methanol, 27-32°).

The percentage composition of the unfractionated mixture was determined as for the previous reaction. By this means, it was found that the less soluble isomer constituted 60% of the reaction product, and the more soluble isomer, 40%.

A similar addition was attempted with *L*-leucine and the

anhydride, by the use of a Schotten-Baumann technique. This yielded only a small amount (30%) of the desired product. Moreover, this was contaminated with a considerable amount of free *beta*-phenylglutaric acid, which was difficult to remove.

Condensation of ethyl phenylmalonate with *levo-alpha*-phenethyl amine produced, as the sole isolable product, only the diamide (m.p. 211-212°), with a yield of about 30%. From a similar reaction with *dextro*-desoxyephedrine, only an alkali-insoluble compound (m.p. 85-86°) could be obtained.

Summary

As a non-enzymatic analog of the asymmetric dehydration of citric acid, a study has been made of the reaction between optically active amines and *beta*-phenylglutaric anhydride, a compound possessing the same type of symmetry as citric acid. It has been found that *levo-alpha*-phenethyl amine adds to *beta*-phenylglutaric anhydride with partial steric selectivity, to produce a high yield (93-95 per cent) of N-*alpha*-phenethyl-*beta*-phenylglutaramic acid. In the unfractionated product, the two diastereoisomeric forms have been shown to be present in unequal amounts, the less soluble isomer constituting 60 per cent of the mixture. Thus an asymmetric reaction, analogous to the asymmetric, enzymatic transformation of citric acid, has been demonstrated in a simple, non-enzymatic, homogeneous system.

VITA

The writer was born on September 5, 1916, in New York, New York, and attended public elementary and high schools in that city. In October, 1931, she entered Barnard College. While there she held a New York State Regents Scholarship. In February, 1935, she received the degree of Bachelor of Arts. During the next two years, she studied, as a part-time student, in the Graduate School of Columbia University and received the degree of Master of Arts in December, 1937. For several years she served as laboratory assistant in physical science in the New York high schools. In September, 1949, she entered the Graduate College of the University of Illinois.